Reducing TB transmission and Improving treatment of Latent TB disease: What is the optimum Strategy?

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Introduction

- Ongoing TB transmission
- Immune Reconstitution Syndrome
- TB preventive Therapy (TBPT)
  - Primary TBPT
  - Secondary TBPT
- Implementation tandem
- Conclusion

Tackling ongoing TB transmission

- Introduction of HAART results in a reduction of TB incidence by as much as 80%
- Efficiency in recruitment of TB patients to ART program *(vs. ANC population)*
  - 1 recruited for every 3 screened *(1:48 in ANC)*
  - Low screening costs: US $36/enrollee *(US $214 for ANC)*
- TB program is a desirable ART entry point
  - High co-infection rates
  - Similar experiences in use of multiple drug regimens
  - Well established TB care infrastructure

Badri M et al, Lancet 2002; Chi BH et al JAIDS 2005

Tackling ongoing TB transmission

- Overall reduction in TB risk while on HAART
  - Risk higher than in general population due to increased survival
- X10 greater risk of recurrent TB in HIV+ vs. HIV- after completion of TB treatment
- Cape Town AIDS Cohort – 5 year TB-free survival is lower in patients:
  - Young age (33 yrs)
  - Low CD4 cell counts (<100cells/μl)
  - Plasma Viral load >= 5 log copies/ml
  - Advanced HIV disease (WHO 3 & 4)

Fitzegrald et al JAIDS 2001; Williams BG, Dye C, Science 2003; Lawn SD et al, AIDS 2005

Tackling ongoing TB transmission

- Difficulties in maximizing enrolment from TB program
  - Immune Reconstitution Syndrome
  - Challenges in implementation TB preventive therapy
  - Timely screening for Subclincial TB disease
  - Program Implementation priorities

Fitzegrald et al JAIDS 2001; Williams BG, Dye C, Science 2003; Lawn SD et al, AIDS 2005

Immune Reconstitution Syndrome (IRS)

- Paradoxical reactions in 36% TB/HIV co-infected on TB Rx and ART
- Occurs 3 months after initiation of ART when there is rapid increase in CD4 cells – redistribution of activated CD45Ro memory cells from Lymphoid tissues
- Increased incidence in presence of other risk factors:
    - Low CD4 cell counts
    - Pulmonary and extra pulmonary disease
- Gugulethu Community Health Centre
    - 24% [9/37] of deaths due to IRS (22% TB deaths;5% of total deaths)

Narita M et al, Am J R CCMed 1998; Wendel KA et al, Chest 2001; Nava et al, Arch Int Med 2002, Lawn SD et al AIDS 2005 & Lancet 2005

Primary TB preventive Therapy

- 30% of HIV infected persons with LTBI will eventually get active TB
- >90% drop in TB incidence by use of IPT
- Relevant in populations with high TB incidence
- TST+ individuals benefit more from TB preventive Therapy than TST- persons (RR: 0.38 vs. 0.83)

Woldehanna S & Volmink J Cochrane database of Systematic Reviews 2006 Issue 1

Primary TB preventive Therapy (2)

- Reduce risk of IRS and of Nosocomial TB transmission in ART clinic
- ?Indication of adherence potential of patient prior to ART
- Preventive therapy vs. Placebo is associated with lower TB incidence but no effect on all cause mortality
- Varied efficacy of TB preventive regimens in high TB re-infection areas
    - INH only – 18 months
    - RIF+PZA or RIF+INH – 3 years

Lambert et al, Lancet Inf Dis 2003, Johnson et al AIDS 2001,

Primary TB preventive Therapy (3)

- South Africa Gold Miners (Overall: N=1655)
  - Intervention: IPT x 9 or 12 months + CPT; No ART
  - TB incidence rate -- Pre-clinic: 11/100 Pyr; Post-clinic: 9/100 Pyr
  - Overall reduction in incidence - 38% (46% in pple with no h/o TB)
  - 78% WHO stages 1 & 2; Mean CD4 = 371 cells/μl (IQR: 252-530)

Effect of Clinic entry on TB incidence:

	Incidence Rate Ratio (95%CI); *P value*
Univariate analysis	0.78 (0.58-1.05); *0.10*
Adjusted for Calendar period & age	0.67 (0.47-0.96); *0.03*
Adjusted for Calendar period, age & WHO stage	0.65 (0.45-0.92); *0.02*

Grant AD et al, JAMA 2005

Secondary TB preventive Therapy

- Reduction in TB incidence by 55 - 80%
  - No significant decrease in mortality
  - TB incidence rates may still remain high
- Life long therapy
  - Adherence difficulties
  - Emergence of resistance
- Effectiveness may be limited to HIV+ persons with one previous episode of TB

Churchyard GJ et al, AIDS 2004

Implementation tandem

- Comprehensive HIV care, Treatment & Management Plan: Initially - centralized, hospital based
  - Plans to include PHCs as ART service points in 2006
- National TB Control Program: decentralized TB services, in the PHCs

Example: Frere Hospital

- Tertiary hospital in East London
- April 2004 - accredited ART service point
- TB screening and Diagnosis but no TB Rx
- By end of Dec ’05 (est)
  - 2,000 enrolled into HIV care & Rx
  - 1,300 (65%) CD4 <200 cells/μl
  - 810 (41%) on ART
- Total on TB & ART = 45 (6%)**
  - Mean baseline CD4: 94 cells/μl (IQR: 111 – 145)
  - Mean age: 32 yrs (missing=3)

**Missing/incomplete data

Example: Frere Hospital

- Initiated ART then TB Rx = 17
  - Mean baseline CD4: 85 cells/μl
  - Mean Age: 33.9 yrs (missing=1)
  - 2 deaths same month of starting TB Rx (?IRIS)
  - Mean time taken to start TB Rx: 110.2 days (range: 0-325)
- Initiated TB then ART = 21
  - Mean baseline CD4: 91.6 cells/μl
  - Mean age: 32 years (missing=1)
  - 1 death (same month of starting ART)
  - I LTFU (7mths after ART initiation)
  - Mean time taken to start ART: 109.7 days (range: 14-245)

Issues for Discussion (1)

- Criteria for primary TB preventive Therapy in advanced HIV disease is unclear
  - Early HIV disease (WHO stage 1 & 2), exclusion of active TB is easier
  - No evidence for preventive therapy in patients with AIDS
- Protective Efficacy of non-Rifampicin preventive therapies decreases with time (?longer duration of primary prophylaxis)
- Scale up of TB preventive therapy needed before any impact can be documented *(resources, time).*

Issues for Discussion (2)

- Constraints in IPT pilot programs need to be addressed:
  - Limited motivation & knowledge of lay workers to discuss TB issues during HIV testing sessions *(capacity development & incentives)*
  - Insufficient medical screening (CXR etc)
- Consideration for Secondary TB preventive therapy

Issues for Discussion (3)

- Screening for sub-clinical TB infection
- Risk Assessment of TB/HIV co-infecetd Patients
  - High risk: Starting HAART within 1st 2 months of antiTB Rx, CD4 <100 cells/μl, PVL > 10^5 copies/ml
- Increase access to ART for all eligible patients with greater emphasis on TB/HIV co-infected
  - Revision of ART eligibility criteria to include WHO stage 3/4 & CD4 <200 cells/μl
  - Adjunctive therapy with TBPT